

PATENT SPECIFICATION

NO DRAWINGS

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COMPLETE SPECIFICATION

Improvements in or relating to Anti-Pepsin Pharmaceutical preparations

- We, EVANS MEDICAL LIMITED, a British company, formerly known as Evans Medical Supplies Limited, of Speke, Liverpool, 19, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
- This invention relates to pharmaceutical preparations and has as an object to provide improved pharmaceutical preparations for the treatment of gastro-intestinal dis-orders and to provide a degraded carrageenin for use therein.
- The precise aetiology of peptic ulceration of the gastro-intestinal tract is still obscure but the evidence that both gastric acid and pepsin are necessary for the formation and maintenance of ulceration is formidable and is widely accepted, the acid providing a low pH at which the proteolytic activity of pepsin is most effective.
- Modern medical treatment of peptic ulcer consists in the main of bedrest and a bland diet, with antacid therapy, sedation and therapy designed to inhibit vagal activity. Progress in treatment during recent years has consisted chiefly in improvements on these lines, and more accurate assessment of the *in vitro* tests relating to the efficacy of this therapy.
- Pepsin is less amenable than gastric acid to the measurement of its quantity, its activity, and its inhibition in the stomach so that while there has been general agreement that it plays an important part in ulcer formation and maintenance, specific treatment designed to inhibit pepsin has been singularly lacking.
- It has for many years been believed (Fogelson, J. Am. Med. Ass., (1931), 96, 673; Babkin and Komarov, Canad. Med. Ass. J., (1932), 27, 463) that gastric mucus had anti-pepsin properties, and most interest has been shown in the fraction of gastric mucus containing sulphated polysaccharide having anti-pepsin activity. This property is not limited to those sulphated polysaccharides which occur most abundantly in the secretions of the human and animal stomach but is also present in substances of similar structure such as heparin (Levy and Sheinfeld, Gastroenterology, (1954), 27, 625; Rosen *et al.*, Proc. Soc. Exp. Biol., N.Y., (1956), 92, 439). Polysaccharides lacking a sulphate group (such as hyaluronic acid) have on the other hand been shown to be devoid of pepsin-inhibiting properties (Levy and Sheinfeld, *loc. cit.*).
- Following extensive laboratory experiments, we have been able to confirm that certain sulphated polysaccharides have a definite pepsin-inhibitory activity.
- Furthermore, Rosen *et al.* (*loc. cit.*) have shown the value of a sulphated polysaccharide in greatly lowering the incidence of induced gastric ulcers in the Shay rat.
- In respect of the naturally occurring sulphated poly-saccharides of marine algal origin or other polysaccharides which following sulphation show antipepsin activity, we have found that fucoidin and degraded carrageenin prepared according to the present invention, inhibit gastric pepsin activity. We have also found that these substances share this property with other naturally occurring polysaccharides, for example, heparin and chondroitin sulphate. They are almost as active (in respect of antipepsin activity) as heparin and considerably more active than chondroitin sulphate. Fucoidin and degraded carrageenin have other properties which make them more desirable than heparin or chondroitin sulphate for example; compared with heparin, fucoidin is less toxic, is generally more stable, is cheaper and is more readily

[Price]

Price

available. Compared with synthetic sulphates of polysaccharides, for example, laminarin sulphate and dextran sulphate, fucoidin and degraded carageenin are less toxic, more stable, much cheaper, and are more readily obtained.

The present invention provides a degraded carageenin which is soluble in water and insoluble in acetone and alcohol, said degraded carageenin forming aqueous solutions of reduced viscosity as compared with commercial carageenin and having the same combined sulphate content as undegraded carageenin, the degraded carageenin being obtained by controlled treatment of commercial carageenin with acid in the presence of an organic liquid followed by the adjustment of the pH to not less than 7 and then by precipitation from its aqueous solution thereof having a pH of 7 to 8 with an organic non-solvent therefor.

The present device also provides pharmaceutical preparations comprising (1) a degraded carageenin according to the present invention or fucoidin, and (2) at least one antacid substance.

The degraded carageenin according to this invention will hereinafter be referred to for the sake of brevity as "degraded carageenin".

The preparations of the present invention may also contain one or more compounds from the following groups of therapeutic substances: (a) antispasmodics, (b) demulcents, (c) pharmacologically active agents which facilitate the repair of tissues, and (d) mood-modifying drugs or sedatives.

The preparations of the present invention may be used in any desired form, for example tablets, powders, granules or liquid preparations, for example suspensions or solutions.

The preparations of the present invention are useful in the treatment of gastro-intestinal disorders such as gastric ulcer, duodenal ulcer, gastritis, hyperchlorhydria and other digestive disturbances.

Fucoidin and degraded carageenin have several advantageous properties; for example they occur naturally in sulphated form; they are the most active (in respect of antipepsin activity) of non-toxic substances of similar nature; they are completely harmless to human beings; the raw materials from which they are obtained are exceedingly abundant; they are very cheap; they are stable; they are soluble in water and gastric juice; they have a bland, not unpleasant taste; they do not interfere with the subsequent digestion of protein by trypsin, and their antipepsin activity is not destroyed by saliva.

Examples of antacids which may be employed are aluminium hydroxide, aluminium glycinate and calcium carbonate. It

will be understood that a mixture of antacids 65 may be used.

The antacid substances employed should not normally raise the pH of gastric contents above about 5, since sulphated polysaccharides will only inhibit peptic activity 70 in acid media.

An example of antispasmodic substance which may be used is atropine sulphate.

Atropine sulphate does not affect the anti-pepsin activity of fucoidin or degraded carageenin. The main purpose of the presence of atropine in the preparation is to decrease the motility of the stomach and to depress the secretion of gastric juice, both of which factors are important in ulcer treatment. Not only does the fucoidin or degraded carageenin inhibit the gastric pepsin but it also combines with gastric tissue protein thereby preventing the access of any residual pepsin to the ulcer crater. 80 85

The presence of an antacid together with fucoidin or degraded carageenin is beneficial because it raises the pH of the stomach contents to a desirable level by buffering gastric acid. It has recently been confirmed by Perry *et al.*, (Proc. Soc. Exp. Biol., N.Y., (1956), 92, 237) that in certain conditions the level of gastric acid and pepsin are to some degree correlated. The most beneficial form of therapy should therefore include both an effective antipepsin agent and an antacid substance or substances such as aluminium hydroxide, aluminium glycinate or sodium bicarbonate. 90 95

Although as normally extracted, fucoidin is obtained as a fawn coloured powder whose solutions are not appreciably more viscous than water, carageenin as normally extracted from *Chondrus crispus* gives solutions which when they contain about 5% of carageenin set to stiff gels. This property is disadvantageous in the preparation of pharmaceutical preparations in the form of liquids and tablets containing carageenin. 100 105

It is well known that the viscosity of these solutions can be reduced or destroyed by heating with dilute mineral acid. But during this process as usually carried out, desulphation also occurs, resulting in a product with diminished antipeptic properties or none at all. 110 115

We have devised a process whereby this reduction in viscosity of the carageenin solution can be effected without desulphation and without loss of antipeptic activity, to provide degraded carageenin. 120

The process is one of controlled treatment with acid, for example mineral acid, in the presence of an organic liquid in which the carageenin is insoluble, for example acetone or alcohol. 125

Carageenin, as normally obtained from Irish moss, is mixed with acetone and to this is added water and mineral acid, for

example hydrochloric acid or other mineral acid, and the mixture is allowed to stand with occasional stirring until a solution of a sample of the carrageenin is of the required viscosity. When this has occurred the mixture is adjusted to pH 7-8 with alkali, for example sodium hydroxide. The carrageenin is then filtered, washed with acetone, dissolved in water, decolorised, and 5 precipitated from solution with acetone or alcohol. The preparation so obtained is re-dissolved in water and re-precipitated with acetone or alcohol and dried. This re-solution and re-precipitation process is repeated until 10 a degraded carrageenin of satisfactory purity is obtained, using techniques known to those skilled in the art.

The essential part of the process is the controlled treatment with acid in the presence 20 of an organic liquid, for example acetone or alcohol.

The following is an example of the preparation of degraded carrageenin:—

25 kilograms of commercial carrageenin (5% w/v solution forms a stiff gel) was mixed with 75 litres of acetone and to this was added a mixture of 3 litres of water and 75 litres of concentrated hydrochloric acid solution and the mixture allowed to stand at room temperature, with occasional stirring, for 24 hours or until solutions of the carrageenin considerably stronger than 5% (for example 30 25% and greater did not gel).

The carrageenin was filtered off, washed 35 with the organic liquid, dissolved in water, the solution adjusted to pH 7 to 8 with alkali, filtered and decolorised by using charcoal or by repeated acetone precipitation, finally precipitated very carefully by pouring 40 slowly into acetone and carefully dried to give degraded carrageenin which is a white powder readily soluble in water and having the same combined sulphate content (viz, ca. 45 30%) and antipeptic activity as the starting material (commercial carrageenin).

The following examples illustrate the invention:—

EXAMPLE I.

30 grammes of fucoidin were mixed with 50 30 grammes of sodium bicarbonate and the mixture granulated by mixing with it 11 millilitres of a solution of 75% ethyl alcohol in water, passing this mixture through a stainless steel sieve and drying the granules so 55 formed at 50° C. 600 milligrammes of stearic acid were added to the granules which were compressed into tablets containing 300 milligrammes of fucoidin and 300 milligrammes of sodium bicarbonate.

Demonstration of Activity (Antipepsin). 60

One of these tablets was dissolved in 60 millilitres of acid solution, the reaction of the solution being pH 1.6. 1 millilitre of this solution, therefore, contained 5 milligrammes of fucoidin and the equivalent of 5 milligrammes of sodium bicarbonate. The test 65 was set up as follows:—

Tube No.	Reaction mixture	
1	P+F+Hb	
2	P+F+Hb	
3	P+FT+Hb	70
4	P+FT+Hb	
5	P+b+Hb	
6	P+b+Hb	

together with appropriate blanks to allow assessment of the contribution to the measured colour of pepsin, fucoidin and haemoglobin separately. 75

EXPLANATION OF SYMBOLS.

P=1 millilitre of pepsin (granular 1: 10000) solution pH 1.6 containing 20 milligrammes of this pepsin in 100 millilitres. 80

b=1 millilitre of hydrochloric acid solution pH 1.6.

F=1 millilitre of fucoidin solution (5 milligrammes/millilitre) pH 1.6. 85

Ft=1 millilitre of solution of tablet. 1 millilitre contains 5 milligrammes of fucoidin and 5 milligrammes of sodium bicarbonate. 90

Hb=1 millilitre of haemoglobin solution (equine) pH 1.6 containing 1200 milligrammes of haemoglobin in 100 millilitres. 95

METHOD.

The pepsin and fucoidin tablet with sodium bicarbonate or acid solution pH 1.6 were pre-incubated in a water bath at 37° C. for 10 minutes and the substrate was then added. Incubation was then allowed to proceed for 30 minutes, after which the tubes were removed from the water bath and 10 millilitres of 10% trichloracetic acid was added to each and the contents shaken. The tubes were allowed to stand for 15 minutes then the contents were filtered (Whatman No. 3, the word "Whatman" being a Registered Trade Mark). 5 millilitres of the filtrate were taken and to this were added 10 millilitres of N—NaOH and 3-millilitres of Folin-Ciocalteu's phenol reagent (diluted 1+2 with water). The blue colour which developed was measured in an absorptionmeter using a red filter. The blue colour developed was proportional to peptic activity over the useful range of optical densities. 100 105 110 115

RESULTS.

Tube No.	Optical density $\times 1000$ corrected for blanks	% reduction in optical density	Mean
5	1 335	49	48
	2 352	47	
	3 332	50	
	4 343		
	5 661		
	6 666	48	

10 The percentage reduction in optical density indicates percentage reduction in peptic activity.

In acid conditions in the human stomach, sodium bicarbonate in appropriate dosage does not affect the antipepsin activity of fucoidin. The purpose of the sodium bicarbonate is to react with excess acid which occurs in gastric conditions which the preparation will be used to treat.

EXAMPLE II.

20 Preparation of degraded carrageenin and aluminium hydroxide in liquid form.

What is usually referred to in pharmacy and medicine as aluminium hydroxide is prepared by reacting a soluble aluminium salt with an alkali and collecting the precipitate. This precipitate is then diluted to give a thixotropic suspension of aluminium hydroxide of known alumina content (usually between 3.5 and 4.4% w/w Al_2O_3).

30 In this example, enough degraded carrageenin, whose preparation is described above, was added to the precipitate of aluminium hydroxide to give the required percentage, 10% or 14% w/w, in the final preparation, together with enough sorbitol to give 1% w/v in the final preparation, and water added almost to volume. The degraded carrageenin and sorbitol dissolved in the water. Flavouring agents and preservative were added in the usual manner and the final volume of the preparation adjusted.

40 The purpose of the sorbitol is to prevent the degraded carrageenin causing the suspension of aluminium hydroxide to gel. Without sorbitol a suspension of aluminium hydroxide containing carrageenin, even of the degraded carrageenin whose preparation is described above, will eventually solidify. In the presence of sorbitol, for example 1% w/v, this solidification will not occur even at reasonably elevated temperatures, for example 45° C. Other substances which can fulfil the same function as sorbitol are organic hydroxy compounds, for example, mannitol, glycerol, citrates and tartrates.

50 Using degraded carrageenin, concentrations of 15% w/v and greater in the aluminium hydroxide suspension can be prepared, the resulting preparation having fluidity convenient for use; whereas incorporating carra-

geenin as normally obtained in commerce, suspensions of aluminium hydroxide of the strength generally used in medicine cannot be prepared to remain in a fluid state and to contain more than about 2% of the carrageenin as normally obtained. This is a great advantage since the frequency of dosage is reduced considerably.

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ANTIPEPTIC ACTIVITY.

The preparation was centrifuged and enough of the supernatant liquid removed. This was diluted with acid solution to contain 5 milligrammes of carrageenin per millilitre.

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75 The test was performed as in Example I, substituting degraded carrageenin for fucoidin and substituting T_3 (1 ml of the diluted supernatant liquid containing 5 milligrams of carrageenin) for FT.

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80 Appropriate blanks and controls were employed.

RESULTS.

85 The percentage inhibition of peptic activity averaged 50% and 52% for T_3 as compared with 49% and 49% for an equivalent amount of the degraded carrageenin itself.

EXAMPLE III.

90 Tablet preparation of degraded carrageenin with dried aluminium hydroxide.

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95 200 grammes of finely powdered degraded carrageenin were mixed with 120 grammes of dried finely powdered aluminium hydroxide and 100 grams of dried starch. Sufficient of a mixture containing 75% of acetone and 25% of water were added and mixed with the powders. The mixture was passed through a sieve of suitable mesh size and dried at 30—40° C. Flavouring and sweetening agents, for example oils of peppermint and spearmint, and saccharin, were added in a manner known to those skilled in the art, preservative, for example benzoic acid, and 16 grammes of talc were added and mixed thoroughly with the granules which were then compressed into tablets containing 500 milligrammes of carrageenin and 300 milligrammes of dried aluminium hydroxide, together with the other constituents of the tablets.

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100 ANTIPEPTIC ACTIVITY.
The tablets were crushed and shaken with

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- water to dissolve the degraded carrageenin. This solution was separated from the water-insoluble material by centrifuging and filtration, and adjusted to contain 5 milligrams of degraded carrageenin per millilitre at pH 1.6. The test was then conducted as described in Example 1, substituting CT for FT where CT=1 millilitre of solution containing 5 milligrammes of degraded carrageenin.
- The percentage inhibition of pectic activity was 52% and 49% for CT, compared with 63% and 62% for an equivalent amount of degraded carrageenin alone.
- Similar results were obtained when the test was conducted at pH 3.5, the approximate pH to which aluminium hydroxide raises gastric contents.
- WHAT WE CLAIM IS:—**
1. Degraded carrageenin which is soluble in water and insoluble in acetone and alcohol, said degraded carrageenin forming aqueous solutions of reduced viscosity as compared with commercial carrageenin and having the same combined sulphate content as undegraded carrageenin, the degraded carrageenin being obtained by controlled treatment of commercial carrageenin with acid in the presence of an organic liquid followed by the adjustment of the pH to not less than 7

and then by precipitation from its aqueous solution having a pH of 7 to 8 with an organic non-solvent therefor.

2. Pharmaceutical preparations comprising (1) a degraded carrageenin as claimed in Claim 1 or fucoidin, and (2) at least one anti-acid substance. 35

3. Pharmaceutical preparations as claimed in Claim 2 also containing one or more compounds from the following groups of therapeutic substances: (a) antispasmodics, (b) demulcents, (c) pharmacologically active agents which facilitate the repair of tissues, and (d) mood-modifying drugs or sedatives. 40

4. Pharmaceutical preparations as claimed in Claim 2 or 3 wherein the antacid substance is aluminium hydroxide. 45

5. Pharmaceutical preparations substantially as described with reference to Example I. 50

6. Pharmaceutical preparations substantially as described with reference to Example II or III.

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PROVISIONAL SPECIFICATION

Improvements in or relating to Anti-Pepsin Pharmaceutical preparations

- We, EVANS MEDICAL SUPPLIES LIMITED, 55 a British company, of Speke, Liverpool, 19, do hereby declare this invention to be described in the following statement:—
- This invention relates to pharmaceutical preparations and has an object to provide improved pharmaceutical preparations for the treatment of gastro-intestinal disorders. 60
- The precise aetiology of peptic ulceration of the gastro-intestinal tract is still obscure but the evidence that both gastric acid and pepsin are necessary for the formation and maintenance of ulceration is formidable and is widely accepted, the acid providing a low pH at which the proteolytic activity of pepsin is most effective. 65
- Modern medical treatment of peptic ulcer consists in the main of bedrest and a bland diet, with antacid therapy, sedation and therapy designed to inhibit vagal activity. Progress in treatment during recent years has consisted chiefly in improvements on these lines, and more accurate assessment of the *in vitro* test relating to the efficacy of this therapy. 70
- Pepsin is less amenable than gastric acid to the measurement of its quantity, its activity, and its inhibition in the stomach so that while there has been general agree- 75
- ment that it plays an important part in ulcer formation and maintenance, specific treatment designed to inhibit pepsin has been singularly lacking. 85
- It has for many years been believed Fogelson J. Am. Med. Ass. (1931) 96 673; Babkin and Komarov Canad. Med. Ass. J. (1932) 27 463 that gastric mucus had anti-pepsin properties, and most interest has been shown in the fraction of gastric mucus containing sulphated polysaccharides having antipepsin activity. This property is not limited to those sulphated polysaccharides which occur most abundantly in the secretions of the human and animal stomach but is also present in substances of similar structure such as heparin (Levy and Sheinfeld Gastroenterology (1954) 27 625; Rosen *et al* Proc. Soc. Exp. Biol. N.Y. (1956) 92 439). Polysaccharides lacking a sulphate group (such as hyaluronic acid) have on the other hand been shown to be devoid of pepsin-inhibiting properties (Levy and Sheinfeld loc cit.). 90
- We have, following extensive laboratory experiments, been able to confirm that certain sulphated polysaccharides have a definite pepsin-inhibitory activity. Furthermore Rosen *et al* (loc cit.) have 100
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shown the value of a sulphated polysaccharide in greatly lowering the incidence of induced gastric ulcers in the Shay rat.

In respect of the naturally occurring sulphated polysaccharides of marine algal origin or other algal polysaccharides which following sulphation show antipepsin activity, we have found, for example, that fucoidin and carrageenin and solid material prepared from aqueous or dilute acid extracts of *Fucus vesiculosus*, *Ascophyllum nodosum*, or of *Chondrus Crispus*, for example, inhibit gastric pepsin activity. We have also found that these substances share this property with other naturally occurring sulphated polysaccharides, for example, heparin and chondroitin sulphate. They are almost as active (in respect of antipepsin activity) as heparin and considerably more active than chondroitin sulphate. Fucoidin has more antipepsin activity weight for weight than carrageenin. Fucoidin has other properties which make it more desirable than heparin, chondroitin sulphate or carrageenin; compared with heparin, fucoidin is less toxic, more stable, has better keeping properties, and is more readily available.

Compared with synthetic sulphates of polysaccharides, for example, laminarin sulphate and dextran sulphate, fucoidin is less toxic, more stable and is more readily obtained.

According to the present invention pharmaceutical preparations are provided comprising (1) marine algae such as seaweed or Irish moss or naturally occurring sulphated poly-saccharide of marine algal origin or other polysaccharides of marine algal origin which have been sulphated and which show antipepsin activity and (2) an antacid substance.

The preparations of the present invention may also contain one or more of the following groups of therapeutic substances (a) anti-spasmodics, (b) demulcents (c) pharmacologically active agents which facilitate the repair of tissues and (d) mood-modifying drugs or sedatives.

The preparations of the present invention may be used in any desired form for example tablets, powders, granules or as liquid preparations for example suspensions or solutions.

The preparations of the present invention are useful in the treatment of gastro-intestinal disorders such as gastric ulcer, duodenal ulcer, gastritis, hyperchlorhydria and other digestive disturbances.

We prefer to use fucoidin as the sulphated polysaccharide. Fucoidin has several advantageous properties, for example, it occurs naturally in sulphated form; it is the most active (in respect of antipepsin activity) of non-toxic substances of similar nature; it is completely harmless to human beings; the raw material from which it is obtained is

exceedingly abundant; it is very stable; it is soluble in water and gastric juice; it has a bland, not unpleasant taste; it does not interfere with the subsequent digestion of protein of trypsin, and its activity is not destroyed by saliva.

Examples of antacids which may be employed are magnesium oxide, aluminium hydroxide, aluminium glycinate and calcium carbonate. It will be understood that a mixture of antacids may be used. Thus for example it is sometimes advantageous to use a mixture of a slow acting antacid with a rapidly acting antacid. Similarly it may be important to offset possible gastric disturbances by one antacid by the incorporation of an antacid substance with an opposing action.

An example of an antispasmodic substance which may be used is atropine sulphate.

Atropine sulphate does not affect the antipepsin activity of fucoidin. The main purpose of the presence of atropine in the preparation is to decrease the motility of the stomach and to depress the secretion of gastric juice, both of which factors are important in ulcer treatment. Not only does the fucoidin inhibit the gastric pepsin but it also combines with gastric tissue protein thereby preventing the access of any residual pepsin to the ulcer crater.

The presence of an antacid together with fucoidin and atropine sulphate is beneficial because it raises the pH of the stomach contents to a desirable level by buffering gastric acid. It has recently been confirmed by Perry et al (Proc. Soc. Exp. Biol. N.Y. (1956) 92, 237) that in certain conditions the level of gastric acid and pepsin are to some degree correlated. The most beneficial form of therapy should therefore include both an antacid and an effective antipepsin agent.

The following example illustrates how the process of the invention may be carried into effect.

30 grammes of fucoidin were mixed with 30 grammes of sodium bicarbonate and the mixture granulated by mixing with it 11 millilitres of a solution of 75% ethyl alcohol in water, passing this mixture through a stainless steel sieve and drying the granule so formed at 50° C. 600 milligrammes of stearic acid were added to the granules which were compressed into tablets containing 300 milligrammes of fucoidin and 300 milligrammes of sodium bicarbonate.

DEMONSTRATION OF ACTIVITY (ANTIPEPSIN).

One of these tablets was dissolved in 60 millilitres of acid solution, the reaction of the solution being pH 1.6. 1 millilitre of this solution therefore contained 5 milligrammes of fucoidin and the equivalent of 5 milligrammes of sodium bicarbonate.

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The test was set up as follows:—

Tube No.	Reaction mixture
1	P+F+Hb
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5	P+FT+Hb
3	P+FT+Hb
4	P+b+Hb
5	P+b+Hb
6	P+b+Hb

10 together with appropriate blanks to allow assessment of the contribution to the measured colour of pepsin, fucoidin and haemoglobin separately.

EXPLANATION OF SYMBOLS.
 P=1 millilitre pepsin (granular 1:10000) solution pH 1.6.
 b=1 millilitre acid solution pH 1.6.
 F=1 millilitre fucoidin solution (5 milligrams/millilitre) pH 1.6.
 FT= 1 millilitre of solution of tablet. 1 millilitre contains 5 milligrammes fucoidin and 5 milligrammes sodium bicarbonate.
 Hb=1 millilitre haemoglobin solution (equine) pH 1.6.

METHOD.

The pepsin and fucoidin (or fucoidin tablet with sodium bicarbonate or acid solution pH 1.6) were pre-incubated in a water bath at 37° C. for 10 minutes and the substrate was then added. Incubation was then allowed to proceed for 30 minutes, after which the tubes were removed from the water bath and 10 millilitres of 10% trichloracetic acid was added to each and the contents shaken. The tubes were allowed to stand for 15 minutes then the contents were filtered (Whatman No. 3 the word "Whatman" being a Registered Trade Mark). 5 millilitres of the filtrate were taken and to this were added 10 millilitres of N—NaOH and 3 millilitres of Folin-Ciocalteu's phenol reagent (diluted 1+2 with water). The blue colour which developed was measured in an absorptiometer using a red filter. The blue colour developing was proportional to peptic activity over the useful range of optical densities.

Results:—

Tube No.	Optical density×1000 corrected for blanks	% reduction in optical density	Mean
50	1 335	49	
	2 352		
	3 332	47	
	4 343		
	5 661	50	
55	6 666	48	49

The percentage reduction in optical density indicates percentage reduction in peptic activity.

60 In acid conditions in the human stomach, sodium bicarbonate does not affect the anti-pepsin activity of fucoidin. The purpose of the sodium bicarbonate is to react with excess acid which occurs in gastric conditions which the preparation will be used to treat.

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